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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Mar Tormo
Ana M. Tari
Gabriel Lopez-Berestein

Serial No.: 08/726,211

Filed: October 4, 1996

For: INHIBITION OF BCL-2 PROTEIN EXPRESSION BY LIPOSOMAL ANTISENSE OLIGODEOXYNUCLEOTIDES

Group Art Unit: 1636

Examiner: R. Schwartzman

Atty. Dkt. No.: UTXC:504/STA

REPLY BRIEF

BOX AF
Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Concurrently herewith, Appellants have submitted an Amendment canceling all claims directed to compositions of matter to simplify and greatly reduce issues for appeal. Assuming entry of Appellants' amendment, the only remaining issue on appeal is the obviousness of the method claims over one combination of prior art. Appellants provide the following Reply to the Examiner's Answer with regard to the claims still pending after entry of Appellants' Amendment.

The Section 103 Rejection

Claims 10-30, 44, and 46 directed to methods of inhibiting proliferation of a Bcl-2-associated disease cell remain rejected under 35 U.S.C. §103(a) as obvious over Abubakr *et al.*, Pocock *et al.*, and Cotter *et al.* in view of Tari *et al.* and in further view of Evan. These references, however, fail to teach or suggest the claimed method of inhibiting proliferation of a Bcl-2 associated disease cell using antisense oligonucleotides associated with neutral lipids. These references also do not provide a reasonable basis for one to conclude that Bcl-2 antisense oligonucleotides in combination with neutral lipids would provide a material therapeutically useful for inhibiting proliferation of a Bcl-2 associated disease cell. Thus, one of ordinary skill in the art would not have had the requisite reasonable likelihood of success. *Amgen, Inc. v. Chugai Pharmaceutical Co.*, 927 F.2d 1200, 1209 (Fed. Cir. 1991) (holding that the examiner must show not only that it would have been obvious to try the suggested combination but also that one of ordinary skill in the art would have had a reasonable likelihood of success). Further, the inventors have surprisingly and unexpectedly demonstrated that methods employing such neutral lipid associations of Bcl-2 antisense oligonucleotides are characterized by less nonspecific toxicity and, therefore, have superior therapeutic value. Specification at page 7, lines 12-22, specification at page 37, lines 3-8, FIG. 1 and FIG. 2; Declaration from inventors Tari and Lopez-Berestein (attached as Exhibit A to Appellants' Appeal Brief).

The Answers' Characterization of the Prior Art is Overly Broad

The Examiner's Answer mischaracterizes the teachings of the cited references, employing hindsight to find the claimed methods obvious.

1. **Abubakr *et al.* Abstract**

The Abubakr *et al.* abstract merely discloses the use of an antisense oligodeoxynucleotide against the translation initiation site of Bcl-2 mRNA in a SCID mouse model for human follicular small-cleaved cell lymphoma. Animals receiving Bcl-2 antisense oligonucleotides reportedly exhibited longer survival and *their pathological examination showed no tumors.* It was hypothesized that the mortality of the antisense-treated animals was due to the toxicity of the antisense to normal tissues and that different dose-schedules or employing an antisense oligonucleotide to a different site of the Bcl-2 mRNA may prevent or minimize toxicity.

The Abubakr *et al.* abstract does not employ or suggest the use of any lipid formulations in general or neutral lipids in particular. Despite recognizing a potential toxicity concern, this reference also does not teach that any lipids, much less neutral lipids, might minimize the toxicity of the antisense oligonucleotide to the normal tissues. In fact, Abubakr *et al.* teaches away from the invention both in teaching (i) that the antisense-treated animals died because of their treatment and (ii) that the potential toxicity problem should be addressed by changing the antisense oligonucleotide or its dose as opposed to changing its form of administration to be an association of the antisense oligonucleotide with a neutral lipid.

This reference also does not teach anything about the effect of a Bcl-2 antisense oligonucleotide on the proliferation of a Bcl-2-associated diseased cell. It only relates to the purported ability of a Bcl-2 antisense oligonucleotide to delay the onset of such a diseased state as evidenced by the reported finding of no tumors in the treated mammals. In contrast, the claimed method requires inhibiting the proliferation of an already diseased cell which is related to treating a subject with existing tumors. The Examiner has provided no rationale for

correlating the former activity purportedly disclosed in the Abubakr *et al.* abstract with the latter claimed method such that one of skill in the art would have a reasonable expectation of success.

2. Pocock *et al.* Abstract

The Pocock *et al.* abstract relates to the use of an antisense oligodeoxynucleotide against Bcl-2 mRNA in a SCID mouse model for B-cell lymphoma. Animals receiving the Bcl-2 antisense oligonucleotides reportedly *failed to develop the lymphoma* relative to sense, nonsense and untreated animals. Examination of the brain, endocrine, and gastrointestinal organs of the Bcl-2 antisense-treated mice apparently showed no adverse toxicity. Thus, the Pocock *et al.* abstract also does not employ or suggest the use of any lipid formulations in general or neutral lipid formulations in particular. Nor does this reference teach anything about the effect of a Bcl-2 antisense oligonucleotide on the proliferation of a Bcl-2-associated diseased cell, merely relating to the delay of onset of diseased state. In addition, the Examiner has provided no rationale for correlating the reported activity with the claimed method such that one of skill in the art would have a reasonable expectation of success.

This reference also does not teach or suggest that toxicity may be a problem inherent in the use of Bcl-2 antisense oligonucleotides, much less teach or suggest the claimed use of neutral lipids to decrease the nonspecific toxicity of lipid-antisense Bcl-2 oligonucleotide associations. In fact, Pocock *et al.* teaches away from the invention in disclosing that the antisense-treated animals did not show any signs of adverse toxicity. Thus, there would be no motivation to modify the formulation administered to the neutral lipid association required by all pending claims.

3. Cotter *et al.* Article

The Cotter *et al.* article apparently relates in more detail the method of the Pocock *et al.* abstract. Animals receiving the Bcl-2 antisense oligonucleotides were said to not develop lymphoma for as long as 40 days. Cotter *et al.* also report, at page 3051, that the finding of a lack of nonspecific toxicity of the Bcl-2 antisense oligonucleotide was purportedly confirmed through the use of a fibroblast cell line. Thus, Cotter *et al.*, as did Pocock *et al.*, does not teach or suggest (i) that a Bcl-2 antisense oligonucleotide may be therapeutically useful to inhibit the proliferation of a Bcl-2-associated diseased cell, (ii) that toxicity may be a problem in the use of certain Bcl-2 antisense oligonucleotides, (iii) the use of any lipid formulations, (iv) the use of neutral lipids, or (v) the unexpected advantage of reduced toxicity when employing neutral lipids in association with Bcl-2 antisense oligonucleotides as required by the claimed methods. In fact, Cotter *et al.* teaches away from the invention for the same reasons Pocock *et al.* teaches away from the invention.

4. Tari *et al.* Patent

The teachings of Tari *et al.* are discussed at length in Appellants' Appeal Brief. However, two points deserve specific mention: (i) Tari *et al.* never addresses the use of any lipid, charged or neutral, with a Bcl-2 antisense oligonucleotide, and (ii) Tari *et al.* never teaches or suggests the surprising and unexpected property of methods employing neutral lipids with a Bcl-2 antisense oligonucleotide to decrease the nonspecific toxicity of the oligonucleotide formulation, but instead teaches that both charged and uncharged lipids are suitable (Tari *et al.*, col. 3, lines 44-50).

5. The Evan PCT Publication

Evan reports on the use of Bcl-2 antisense oligonucleotides to purportedly suppress the expression of the *Bcl-2* protein in *in vitro* studies. Although Evan indicates that *in vivo* use may

be with liposomes, the references cited by Evan in this regard, at page 59, employ only charged liposomes, thus teaching away from the present invention. Further, Evan never discloses that neutral lipids should be employed or would be preferred, much less that associations of Bcl-2 antisense oligonucleotides with neutral lipids would be less toxic than similar associations with charged lipids. In fact, to the extent Evan discusses the toxicity of methods of inhibiting Bcl-2 expression, Evan teaches away from claimed methods and the need for neutral lipid associations having reduced toxicity by stating, at page 59, that "inhibiting *bcl*-2 is not especially likely to be toxic to bystanding cells even if it enters them."

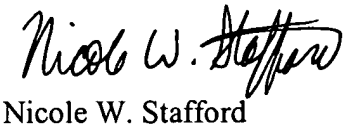
Thus, the only references disclosing the results of therapeutic methods employing Bcl-2 antisense oligonucleotides wholly fail to teach or suggest the use of lipids at all, much less the neutral lipids of the present invention or the surprising and unexpected results found by the Appellants and associated with the claimed methods. Further, the Evan reference, which deals primarily with methods of inhibiting *Bcl*-2 expression *in vitro,* indicates that liposomes in general may be used for *in vivo* applications but provides no specific information regarding the nature of the liposome nor any motivation to select an uncharged versus a charged lipid or to select a less toxic lipid association, and, in fact, cites references which employ charged lipids.

Conclusion

Appellants submit that the issues raised in the Answer with respect to obviousness have been fully addressed in the main Brief and the foregoing Reply. It is submitted that Appellants' have fully demonstrated that the Examiner has failed to make a *prima facie* case of obviousness, based upon a consideration of the prior art and the prevailing case law.

In light of the foregoing comments, appellants submit that the appealed claims meet the requirements for patentability. Therefore, appellants respectfully request that the Board reverse the pending obviousness rejection.

Respectfully submitted,



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